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VIRUS-CARCINOGEN INTERACTIONS[1]

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INTRODUCTION

Since the early studies of Rous and Kidd (60, 61) and Rous and Friedewald (59) and of F. Duran-Reynals and Bryan (23) reporting synergistic effects of chemical carcinogens and, respectively, tumor viruses and nontumor viruses, investigators in the field of cancer virology have gradually become increasingly aware of the possible biological significance of these interactions.

Studies on combined effects of a wide variety of viruses and chemical carcinogens in intact animals have recently been reviewed by M. Duran-Reynals (24). The primary purpose of this paper is to review a parallel literature dealing with these interactions at a cellular level. Recent experimental findings in molecular biology, genetics, and virology have begun to shed light on the nature and mechanism of these interactions and have served to re-emphasize the significance of the earlier studies in intact animals.

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IN VIVO INTERACTIONS

Hydrocarbon Carcinogens and Viruses

Beginning with the earliest studies of interactions of herpes simplex virus and tar in rabbits and guinea pigs (73), numerous investigators have reported instances in animals in which simultaneous or sequential challenge with a virus and a carcinogen has resulted in significant enhancement of the effects of either or both (24). With possible rare exceptions, no evidence has as yet been adduced from such studies that the carcinogen of a pair effects any fundamental biological change in the properties of the virus or that, conversely, the virus of a pair alters in any fundamental way the nature of the neoplastic response to the carcinogen. Synergistic effects therefore constitute, essentially, either reductions in the 50% infectious dose of the virus for a given tissue end point, or reductions in the 50% tumor-inducing dose of the carcinogen.

Tumor viruses. The neoplastic potential of the Shope papilloma (59–61), rabbit fibroma (2), Rous sarcoma (15), and polyoma viruses (57) is enhanced to some degree by combined carcinogen treatment under various experimental conditions (24). These effects are manifested principally as

earlier-appearing or more extensive tumors as a result of a given virus dose, as significant localization of virus-induced tumors to the site of carcinogen application, or as in vivo activation of an otherwise latent oncogenic virus (24).

Nontumor viruses. Under specified experimental conditions, significantly enhanced neoplastic responses have followed concurrent exposure to hydrocarbon carcinogens and to vaccinia, myxoviruses, West Nile virus, and enteroviruses.

In a series of experiments in cortisone-treated mice, F. and M. Duran-Reynals and collaborators (21, 22, 24, 25, 64) observed that the intradermal injection of large doses of vaccinia virus into methylcholanthrene-painted skin resulted in an incidence of local cutaneous fibromyosarcomas and of systemic lymphomas significantly higher than that in carcinogen-painted mice which had been identically injected with an appropriate virus-free control suspension. Moreover, prior immunization of the mice with vaccinia effectively prevented the increased incidence of local and systemic neoplasia (24).

Evidence that experimental infection with influenza virus increases the rate of appearance of lung tumors consequent to treatment with urethane was first reported by Imagawa, Yorhimori, and Adams (34). Many workers had previously shown that, although commonly followed by a transient phase of bronchial and alveolar epithelial proliferation, influenza in the mouse is not associated *per se* with any significant neoplastic response (41, 66, 69, 75). In a series of well-controlled studies, Kotin and Wiseley (37) observed the response of polyoma-free mice to consecutive infections with immunologically distinct respiratory myxoviruses (influenza A, PR-8 strain; influenza B, Lee strain; and parainfluenza 1, Sendai strain), to aerosol exposure to ozonized gasoline (a hydrocarbon-rich carcinogenic mixture), and to both. The consecutive myxoviral infections elicited degrees of squamous and alveolar hyperplasia and metaplasia. The ozonized gasoline, as shown previously (36), produced a low incidence of alveologenic carcinomas in this strain of mice (C57 black) known to be relatively resistant to pulmonary tumor induction. Following exposure of the survivors of consecutive myxoviral challenges to the ozonized gasoline, there occurred, in addition to the separate lesions associated with each stimulus alone, invasive neoplastic lesions virtually indistinguishable from squamous cell carcinoma. Prior to these studies, only relatively massive exposure to hydrocarbon carcinogens (3, 4, 65) or to gamma radiation (29) had produced in rodents lung lesions similar to squamous carcinoma.

Studies in mice by Tanaka and Southam (71) with West Nile virus—selected because of its negligible tendency to elicit cellular proliferative responses—and with methylcholanthrene demonstrated a significant degree of synergism. Virus administered intraperitoneally after 7 of a series of 10 skin-paintings with the hydrocarbon, though unaltered in infectivity or virulence, was associated with a significantly higher incidence of cutaneous neoplasms than occurred in similarly painted, uninjected or sham-injected control mice.

Studies in the writer's laboratory (44) with concurrently administered hydrocarbon carcinogens (9,10-dimethylbenzanthracene-1,2; 2-amino-fluorene; 1,2,5,6-dibenzanthracene) and common human viruses (vaccinia, poliovirus 2, ECHO 9, Coxsackie B_4) indicated a significant association between malignant tumor production and administration of virus-carcinogen pairs, rather than of virus or carcinogen alone. The mice used were shown to be free of polyoma virus infection, and the doses of carcinogens administered were judged to be too small in themselves to induce tumors (63). Prior immunization of the mice against vaccinia caused a probably significant reduction ($P = 0.03$) in the incidence of malignant tumors after concurrent administration of vaccinia virus and 9,10-dimethylbenzanthracene-1,2 (44).

Bacteriophage. Because of the metabolic, genetic, and microbiological complexities of studies in the intact laboratory animal, further analyses in the writer's laboratory of phenomena of virus-carcinogen interaction have been attempted in simpler biological systems (43).

On the assumption that a mutant in a bacterium is analogous to a tumor in a mouse, the mutagenicity of 9,10-dimethylbenzanthracene-1,2 (DMBA) was studied in a bacteria-bacteriophage system, by use of a phage-sensitive strain of *Escherichia coli* B and a virulent coliphage T_5.

Bacteria were grown, and bacteriophage were propagated, in a protein-free aqueous medium containing physiological concentrations of common salts, ammonium ion as the source of nitrogen, and 1% glycerol as the source of

carbon and as a vehicle for DMBA. (The extreme insolubility of most carcinogenic polycyclic aromatic hydrocarbons in aqueous media has seriously hampered studies of these compounds under physiological conditions by many workers. Although water-insoluble, DMBA was found to exist in 1% glycerol in a metabolically available state, primarily as a finely dispersed colloid, and to a slight extent, as a dialyzable solution.)

When propagated in bacteria grown in the presence of DMBA-*9-C*^{14} (5 to 500 $\times$ 10^{-8} M), coliphage T_5 bound carcinogen in amounts proportional to DMBA concentration. Uptake ranged from 12,000 to 970,000 molecules of DMBA per plaque-forming unit (PFU) of bacteriophage. Repeated washings with cold ethyl ether, in which DMBA is moderately soluble, removed most of the carcinogen, leaving from 3 to 15% firmly bound.

The distribution of DMBA-C^{14} in fractions of a suspension of T_5 propagated in *E. coli* B in the presence of the carcinogen was compared with that in fractions of a control suspension of *E. coli* B grown identically and comparably lysed by sonic vibration. Binding of DMBA-C^{14} by T_5—both weak and firm—was significantly higher than that by the *E. coli* sonic extract. After ultracentrifugation and phenol and ether extractions, it was concluded that roughly 90% of the carcinogen bound to T_5 was weakly bound to bacteriophage protein, and 10% was firmly bound to bacteriophage nucleic acid, the latter in a ratio as high as one carcinogen molecule per 500 nucleotide base pairs.

Studies of the mutagenicity of DMBA, both free and bound to T_5, were performed by observing the effect of the carcinogen on the rate of emergence of bacteriophage-resistant bacterial mutants in a phage-sensitive population of bacteria. Bacteriophage and bacteria were rapidly mixed in liquid soft agar and poured on the surface of nutrient agar plates. After 18 hr of incubation (and more than one cycle of bacterial growth), phage-resistant bacterial mutants were seen as surviving bacterial colonies. These colonies were then proven to be resistant to attack by T_5.

After 4 hr of growth in the presence of various concentrations of DMBA, cultures of *E. coli* B were mixed with carcinogen-free T_5. In cultures grown in the presence of 280 $\times$ 10^{12} molecules of free carcinogen per ml, the phage-resistant mutation rate, expressed as mutants per 10^7 bacteria in the original inoculum, was significantly higher than that in the DMBA-free cultures, and approximately doubled.

T_5 containing only weakly-bound DMBA was prepared by incubating suspensions of the bacteriophage in bacterial growth medium containing carcinogen, and then sedimenting and twice washing the bacteriophage in fresh medium. Such weakly bound, ether-extractable DMBA, despite considerable binding (as much as 84,000 molecules per PFU), possessed only a very low mutagenicity.

In contrast, there occurred highly significant increases in bacteriophage-resistant bacterial mutation rates after attack by ether-washed T_5 containing as few as 13,000 firmly bound DMBA molecules per PFU. Comparison of mutation-rate doubling concentrations, in molecules of carcinogen per milliliter, suggested that DMBA firmly bound to T_5 is roughly 100-fold more mutagenic than either free or weakly bound carcinogen (43).

Hydrocarbon Carcinogens and Nucleic Acids

Although interactions of carcinogens and tissue proteins have been the subject of intensive study for over a decade (31, 47), interactions of carcinogens with tissue nucleic acids have received scant attention.

Early studies by Weist and Heidelberger (79–81), using 1,2,5,6-dibenzanthracene-*9,10-C*^{14} of low specific activity, and by Miller and Miller (46), using unlabeled azo dyes, had failed to demonstrate uptake of carcinogens by skin or liver nucleic acids in any way comparable to that by tissue proteins. Reinvestigation of the problem by Davenport (18) and by Heidelberger and Davenport (32) with the use of C^{14}-labeled hydrocarbon carcinogens of higher specific activity demonstrated clearly a firm binding by tissue deoxyribonucleic acid (DNA) in vivo, to a degree exceeding that by tissue protein, on a weight basis.

Possible Interpretations of In Vivo Interactions

Precise interpretations of interactions of hydrocarbon carcinogens with viruses and nucleic acids in the intact animal are complicated by the multiple biochemical and physiological responses to the separate challenges; the profound effects of age, sex, and genetic strain on the nature and

extent of the response; and the possible effects of potentially carcinogenic factors already present in the experimental system—indigenous benign or oncogenic viruses, dietary factors, etc.

The steadily lengthening list of indigenous benign and oncogenic agents identifiable in laboratory animals (58, 62) and of exogenous agents commonly contaminating virus suspensions prepared by passage through tissue cultures or through other animals (68) presents a serious barrier to accurate analysis of the results of any given experiment. Interpretation of the results of studies of virus-carcinogen interactions in the writer's laboratory, for example (44), is complicated by the recent demonstration by Toth (74) that malignant lymphomas of the stem cell type induced in Swiss mice by injection of 7,12-dimethylbenzanthracene were serially transmissible by cell-free filtrates to newborn mice of the same strain.

Attempts to analyze in vivo combined effects in simpler biological systems are based on the assumption that carcinogenesis and mutagenesis are one and the same phenomenon. Although Barratt and Tatum (5) and Tatum (72) showed a strong correlation between the carcinogenicity of various hydrocarbons and their mutagenicity in *Neurospora*, the identity of these effects has been disputed by Burdette (14).

The speed with which mutagenic effects occur and can be quantitated in bacterial and mycological systems, compared to the relatively long latent periods commonly preceding overt tumor induction in animals (63), as well as the relative ease with which these systems can be shown to be free from indigenous or inapparent agents (1), should prompt further exploration of their usefulness in the field of experimental neoplasia.

At the present time, no published investigation entirely excludes any of the following possible interpretations of in vivo interactions of hydrocarbon carcinogens and viruses.

(i) Virus or carcinogen or both act at a distance from the potentially neoplastic target cell: (a) virus infection impairs normal systemic metabolism and excretion of carcinogen, heightening the local tumorigenic effect of a carcinogen dose; (b) through effects of the virus on host resistance, an indigenous virus is activated; or (c) toxicity of carcinogen, in terms of depression of bone marrow, adrenal cortical stimulation, and inhibition of antibody formation, allows an otherwise suppressed oncogenic virus to emerge, propagate, and produce overt neoplasia.

(ii) Virus and carcinogen act synergistically at the level of the target cell: (a) virus attack and injury enhances permeability of cell to carcinogen; (b) virus infection of the cell, though abortive, interferes with normal intracellular detoxification of carcinogen; (c) cells proliferating or regenerating rapidly in the wake of the cytopathic effects of viral infection are more likely to incorporate carcinogen than are relatively quiescent cells; or (d) carcinogen inhibits cellular interferon production (19), and permits emergence of a latent oncogenic virus.

(iii) Direct carcinogen-virus interaction: (a) carcinogen produces an oncogenic virus mutant in a population of otherwise benign virus particles; or (b) virus functions as a vector, facilitating entry of carcinogen into the cell, or delivering carcinogen directly to susceptible intranuclear chromosomal loci (43, 44).

IN VITRO INTERACTIONS

Hydrocarbon Carcinogens and Viruses

Mammalian viruses. Upon incubation of purified high-titer suspensions of poliovirus 2 with solutions of DMBA-C^{14} in acetone, there occurred significant uptake of DMBA by the virus (44). Three separate measurements of uptake, in molecules per $TCID_{50}$, were: 17,000 ± 5,000; 20,000 ± 12,000; and 3,100 ± 900. In similar experiments with vaccinia, and with vaccinia and poliovirus nucleic acids, binding of DMBA was not demonstrated. Although of considerable theoretical interest, the significance of these findings is equivocal, because the in vitro incubation procedure largely inactivated the virus, and in view of the results of subsequent studies with bacteriophage, discussed below.

Bacteriophage. As described earlier, direct in vitro incubation of coliphage T_5 with DMBA-C^{14}, although giving rise to considerable binding, produced only a weakly-bound preparation, possessing minimal mutagenic activity with respect to the host bacterium. Under the conditions of study, neither weakly bound DMBA nor firmly bound DMBA (produced by propagating T_5 in the presence of the carcinogen) exerted detectable mutagenic effects on the bacteriophage itself.

In contrast, with the use of various mutagenic water-soluble acridines, in a system which per-

mitted both in vivo and in vitro uptake, Orgel and Brenner (50) demonstrated induction and reversion of a variety of coliphage T_4 mutants. Effects, if any, of free and phage-bound acridines on host bacterial-mutation rates were not reported.

Since the planar mutagenic acridines serve to a degree as models for an understanding of the mutagenic action of the similarly relatively planar polycyclic hydrocarbon carcinogens, the kinds of mutagenic effects observed by Orgel and Brenner (50) are of some significance. Confirming the findings of Freese (26, 27), they observed that mutations induced by base analogues such as 5-bromouracil or 5-bromodeoxyuridine and those induced by the planar acridines were in two mutually exclusive classes, and were thus produced by different mechanisms at different gene sites. Proposed mechanisms for the interactions of planar acridines and polycyclic hydrocarbons with nucleic acids—mechanisms which do not involve direct replacement of purine or pyrimidine bases—are discussed below.

Hydrocarbon Carcinogens and Nucleic Acids

Nucleic acids of bacteriophage and of higher species. As noted previously, studies in the writer's laboratory suggest that the mutagenicity of bacteriophage-bound DMBA is enhanced only when the carcinogen is firmly bound to bacteriophage DNA (43). Maximal mutagenic effects on host *E. coli* B were observed when approximately 20,000 molecules were firmly bound per coliphage T_5 PFU, a ratio of roughly one carcinogen molecule per 500 nucleotide base pairs.

Higher degrees of uptake of acridines by the DNA of intact bacteriophage have been observed (50), despite evidence that the DNA of the coliphages is so tightly coiled within its protein coat that, theoretically, little space is available in which to fit large numbers of polycyclic molecules (35).

Interactions of polycyclic hydrocarbon carcinogens with the nucleic acids of higher species have been studied intensively by several workers (17). Since the findings so closely parallel those with the more extensively studied mutagenic planar acridine dyes, both sets of findings are perhaps best considered as belonging to the same class of reactions.

Solubility and binding studies by Booth et al. (7) with 3,4-benzpyrene, and by Booth and Boyland (6) with dibenzocarbazoles and dibenzacridines were the first to suggest that polycyclic hydrocarbon carcinogens may bind to DNA. Subsequent studies with similarly planar water-soluble dyes, principally acridines (10, 11, 38, 39, 42, 51, 52, 67), have added much to our knowledge of the general mechanisms of interaction of planar molecules and nucleic acids.

Upon shaking microsuspensions of polycyclic carcinogens and aqueous solutions of highly purified DNA from calf thymus and from rat liver, Boyland and Green (9) observed uptakes of the order of one benzpyrene molecule per 90 nucleotide base pairs, and one pyrene molecule per 30 base pairs; uptake was reduced 75 to 85% in 0.1 M solutions of sodium chloride. Uptake by rat liver ribonucleic acid (RNA) and by heat-denatured DNA was considerably less, suggesting that an intact double-helical DNA structure is necessary for full binding. The authors felt that the carcinogen was relatively loosely bound, because there was virtually quantitative recovery upon extraction of the complex by cyclohexane.

Similar studies by Liquori et al. (40), equilibrating microcrystalline suspensions of benzpyrene and 1,2,5,6-dibenzanthracene with highly polymerized calf thymus DNA, revealed less binding (about 1 benzpyrene molecule per 1,000 base pairs) except under conditions of dilution-denaturation of DNA, in which instance binding was increased. Unlike Boyland and Green (9), they observed increased binding with progressive thermal denaturation of the DNA; like them, they observed only loose binding.

Recent critical studies by Giovanella, McKinney, and Heidelberger (30) have cast doubt on the validity of the experimental methods and conclusions of Boyland and Green (9) and Liquori et al. (40). Repeating the experiments of these workers, Giovanella et al. (30) showed that DNA failed to solubilize polynuclear hydrocarbons in the microcrystalline form.

Studies in the writer's laboratory with calf thymus DNA and DMBA-C^{14} (as a colloid in 1% glycerol) in 0.15 M sodium chloride solutions suggested two forms of carcinogen-binding—one weak and one firm, with respect to ether extractability—and two separate effects of thermal denaturation. Under the experimental conditions, highly polymerized DNA bound about 1 DMBA molecule per 5,000 nucleotide base pairs; only about 25% of the carcinogen was firmly bound.

With increasing degrees of denaturation, total bound carcinogen progressively increased, but firmly bound, ether-fast DMBA virtually disappeared. It was concluded that an intact DNA double helix is a prerequisite for firm binding of the type associated, in bacteriophage, with enhanced mutagenicity of DMBA (43).

Nature of interactions. Studies in 1938 by Brock, Druckrey, and Hamperl (13) and in 1946 by Weil-Malherbe (78) on the solubilization of polycyclic hydrocarbons by various purines suggested that the water-soluble complexes which resulted were built up in a sandwich-like configuration. Similar, more detailed binding studies with purines by Boyland and Green (8) strengthened this hypothesis; those studies by Boyland and Green (9) and Liquori et al. (40) with hydrocarbons and DNA suggested a similar stacking mechanism, in contrast to a nonspecific external surface attachment mechanism. Because of the observed requirement of an intact helix for binding, Boyland and Green (9) rejected a simple stacking mechanism involving one strand, and favored the alternative of intercalation between adjacent base pairs. In contrast, Giovanella et al. (30) cited X-ray diffraction evidence which strongly challenges the intercalation concept.

To the extent that binding experiments with water-soluble planar acridines reasonably describe the nature of the interaction between insoluble, relatively planar polycyclic hydrocarbons and DNA, the observations of Lerman and collaborators (38, 39, 43) lend support to the concept of intercalation between adjacent base pairs. In a series of ingenious experiments, he measured the effects of various acridines on several physical properties of DNA (viscosity, sedimentation coefficient, X-ray diffraction pattern, flow dichroism) and, by measurement of polarized fluorescence, determined the plane of the bound acridine molecules with respect to the axis of the double helix. He interpreted the experimental evidence as indicating that, when complexed with acridines, DNA (i) possessed a reduced mass per unit length; (ii) showed closer packing of molecules of the polymer; (iii) retained the 3.4 Ångstrom spacing along the helix; (iv) assumed a strained, straighter configuration; and (v) lost its regular helical structure (38, 42). In addition, the spatial orientation of the nucleotide bases around the axis of the helix was unchanged by complexing, and the bound acridine molecules were shown to be perpendicular to that axis (39).

He concluded that of the three possible modes of binding, only intercalation of the acridine in a plane perpendicular to the axis of the helix, with consequent unwinding and lengthening of the DNA molecule, fully satisfied all the experimental evidence (38, 39, 42). Moreover, the possibility of displacement of a base pair was excluded (38).

Noting that Peacocke and Skerrett (52) had previously shown that proflavine combines strongly with DNA in a first order reaction to a limit of one dye molecule per four or five nucleotides, and then weakly, to a limit of one dye molecule per nucleotide, and observing that his experimental conditions permitted negligible second-order binding, Lerman concluded that the intercalation hypothesis described the primary, strong-binding process (38).

Properties of carcinogens possibly related to nucleic acid binding. Several mechanisms have been proposed to explain the forces responsible for the binding of polycyclic hydrocarbon carcinogens to nucleic acids. It is, indeed, astonishing that such large, highly insoluble, nonpolar molecules, so characteristically devoid of specific binding sites or groups, should become intercalated in a DNA helix.

Boyland and Green (9), drawing inferences from their studies with benzpyrene and purines (8), somewhat favored the view that polarization or van der Waal's forces were involved, as suggested by Booth et al. (7). Boyland and Green (9) emphasized, however, the possible role of charge-transfer effects; although they looked for and did not find ultraviolet spectral changes indicative of such effects, they noted that their observations did not exclude them.

The concept of charge-transfer, as developed by Pullman and Pullman (53–56) and by Hoffman and Ladik (33) postulates, in polycyclic aromatic hydrocarbons, the presence of a strong, electron-rich, reactive "K-region" and of a relatively inactive "L-region." The concept was developed in relation to theories presupposing the crucial relationship of protein-binding to carcinogenesis (31, 47), and has received strong support from experiments demonstrating that chemical substitutions in the K-region tend to diminish carcinogenic activity and protein-binding, and in the L-region, to enhance these effects (49).

In this regard, Nash (48) and Mason (45) have

proposed that carcinogenic properties are related to the ability of certain polycyclic hydrocarbons to accept electrons from the highest-filled energy band of target proteins.

More recently, however, Szent-Györgi, Isenberg, and Baird (70) have drawn attention to the electron-donating properties of carcinogens, and described a correlation between carcinogenesis and the ability to form charge-transfer complexes associated with the release of an electron.

SIGNIFICANCE OF INTERACTIONS

Theories of Carcinogen Mutagenesis

The development of increasingly precise knowledge of the interaction of mutagens with nucleic acids and bacteriophage has stimulated correspondingly more precise theories of mutagenesis—hypotheses which make full use of the biochemical implications of the Watson-Crick structure of DNA (76, 77), and which incorporate current concepts of genetic coding as related to nucleotide base-pair sequences (16).

The theory of Freese (27) postulated two mutually exclusive classes of mutations, only one of which is inducible or revertible by base analogues. Brenner et al. (12) extended this concept and theorized that the other class, constituting the spontaneous type and those inducible and revertible by acridines, were caused not by altering the nature of base pairs but by insertion-deletion errors in the base-pair sequence. Such errors would tend to be revertible by other insertions or deletions at a distance along the helix; one need not necessarily invoke the action of closely linked suppressors within a gene to explain reversion (12).

Lerman (39) interpreted the mechanism of acridine mutagenesis somewhat differently. In contrast to Brenner et al. (12), whose mechanism of insertion-deletion essentially presupposes alteration of one strand of the DNA molecule, Lerman (39) proposed a hypothesis which he felt was more compatible with the concept of intercalation, and more consistent with the fact that spontaneous mutations and acridine-induced mutations fall in the same class.

He postulated that insertion-deletion effects, as described in the schema of Crick et al. (16), would most easily be manifest in relation to the events of recombination. When a planar dye is intercalated at a site in only one of a pair of chromosomes, he hypothesized, the pairing will be shifted exactly one or more steps out of register. If the chromosomes break at the same position, exchange partners, and reunite, then, "the reunion will result in the omission of one or more base pairs in one product and the corresponding duplication of one or more base pairs in the other product of the reunion" (39), and the mechanism will be closely related to the frequency of crossing-over. He noted that similar explanations of spontaneous mutations through the formation of short loops in the double helix or through unequal crossing-over have been suggested, respectively, by Fresco and Alberts (28) and by Demerec (20).

Possible Role of Viruses

It would be distinctly premature, at this point, to attempt to extrapolate *pari passu* the results of observations in well-defined biophysical and bacteriophage systems to the immensely more complex animal systems in which virus-carcinogen interactions have been studied, or, indeed, to man.

In the face of abundant quantitative epidemiological evidence linking many forms of human cancer to exposure to environmental carcinogens, together with an almost total lack of direct evidence linking human cancer with oncogenic viral agents, more detailed analysis of the role of common, nontumor viruses in enhancing chemical carcinogenesis appears to be of importance.

None of the several possible modes of virus-carcinogen interaction discussed earlier can be excluded at this time, although the findings in simple biological systems lend support to only a few. It would appear that the single or several roles of viruses in the human neoplastic process—as carcinogens, co-carcinogens, or as vectors—will, in the future, most fruitfully be analyzed in simple, definable experimental systems which are susceptible to controlled, quantitative mutagenic analysis.

SUMMARY

Studies on the interactions of polycyclic aromatic hydrocarbon carcinogens with viruses and nucleic acids in vivo and in vitro are reviewed and compared. Increasingly precise measurements in simple biological systems have begun to suggest, in molecular and genetic terms, the significance and implications of such interactions in intact animals.

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